

1,2,3-Trichloropropane

CAS #96-18-4

Swiss CD-1 mice, at 0.0, 30 mg/kg, 60 mg/kg, 120 mg/kg by gavage in corn oil

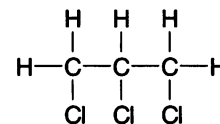
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1, 2, 3-Trichloropropane (TCP), a common industrial solvent and chemical intermediate, was tested for its effects on reproduction and fertility in Swiss CD-1 mice because of the lack of available reproductive toxicity information and the structural relationship to known halogenated propanes dibromochloropropane and α -chlorohydrin. The present study used the RACB protocol. Data from a previous 90-day study and a preliminary 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation phase at 30, 60, and 120 mg/kg/day by gavage in corn oil.

In Task 2, two, two, one, and two mice died in the control through high dose groups; three of these deaths were known to have been due to gavage error. There were no differences in body weights between control and treated F_0 mice, though mice in the middle and high dose groups did consume more water than controls by approximately 12 to 14%.

Fertility effects started manifesting at the third litter; by the last litter, the proportion of pairs delivering a litter was (control to high dose) 87, 78, 68, and *42%, respectively (* indicates significantly different from controls). Aggregate data for Task 2 showed at the high dose a 16% decrease in the number of litters per pair, 47% fewer pups per litter, although no change in pup viability or adjusted body weight. Also at the high dose, the days to delivery of the last two litters were increased by 6 and 4 days.

The last litter was reared by the dam until weaning and then begun on TCP exposure through mating at approximately postnatal day 74. Neither pup weight nor viability were adversely affected by TCP exposure during the nursing period; in fact,

high dose F_1 pups weighed more than their controls, probably because of smaller litters.

The adverse effects on reproductive indices during Task 2 prompted an attempt to determine the affected sex using the control and high dose animals in the Task 3 crossover mating. Neither group containing a treated partner differed significantly from the controls in their ability to mate or deliver live offspring. Litter size, pup viability, and pup weight were not statistically different from controls, although litters from treated females averaged 5 pups per litter, while control litters and those from treated males averaged 9 to 10 pups per litter.

After crossover litters were evaluated and discarded, the control and high dose F_0 mice were killed and necropsied. While male body weight was not different between the two groups, adjusted liver weight was 20% greater in the treated males. Treated males also had approximately 19% more sperm per milligram cauda epididymis than their controls; reproductive organ weights and other sperm indices did not differ between the groups. For females, body weights were not different, but the liver of treated females weighed approximately 22% more than control, while kidneys weighed approximately 9% less. The estrous cycle did not differ in length or frequency of the various stages, although ovary weight was reduced in the treated females by approximately 20%. Four of 10 high dose-treated females had microscopic ovarian amyloidosis versus 0 of 10 controls. No other microscopic lesions were related to TCP exposure.

For the F_1 mating trial there were 20 mating pairs at all dose levels except the high dose, which had 9 because of the reduced litter sizes in Task 2. Only 3 of these 9 pairs delivered a litter with any pups. Though control litters averaged 10.8

pups and the high dose litters averaged 7.3 pups, the difference was not statistically significant, probably due to the low number of litters at the high dose (3 litters). No other end points differed significantly from control for any dose group, including dam weight or days to deliver.

After the delivery of the F_2 litters, the F_1 adults were killed and necropsied. Male body weight was increased by 5 and 11% at the middle and high dose levels, respectively. Adjusted liver weight was increased at these dose levels by 9 and 28%, while adjusted kidney weight was increased at the high dose by 14%. Reproductive organs and sperm indices were unchanged. Female body weight was increased by 9% at both the middle and high dose levels, while adjusted liver weight was increased by 6 and 21%. Female kidney weights were unchanged. Ovary weights showed a monotonic reduction: ovary weight was 15 and 40% lower than controls in the middle and high dose groups. Interestingly, estrous cycle length was increased for all dose groups: from control to high dose, cycle length means were 4.66, 5.08, 5.18, and 5.06 days. There were no significant microscopic lesions noted in female organs.

Thus, this study found significant reproductive toxicity in Swiss CD-1 mice exposed to TCP. This was expressed in the first generation as fewer litters and fewer pups per litter, and in the second generation as fewer fertile matings and reduced ovary weight and lengthened estrous cycles. The F_1 ovary weight reduction and cycle increase occurred in the absence of a change in any measure of "general" toxicity or clinical signs, suggesting that TCP may be a selective female reproductive toxicant. Further studies would be helpful to refute or confirm these effects.

1, 2, 3 - TRICHLOROPROPANE

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

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Chemical: 1,2,3-Trichloropropane

CAS#: 96-18-4

Mode of exposure: Gavage in corn oil

Species/strain: Swiss CD-1 mice

F ₀ generation	Dose concentration →	30 mg/kg	60 mg/kg	120 mg/kg
General toxicity	Male, female	Male, female	Male, female	Male, female
Body weight	—, —	—, —	—, —	—, —
Kidney weight ^a	•	•	—, ↓	—, ↓
Liver weight ^a	•	•	↑, ↑	↑, ↑
Mortality	—, —	—, —	—, —	—, —
Feed consumption	•	•	•	•
Water consumption	—, —	↑, ↑	↑, ↑	↑, ↑
Clinical signs	—, —	—, —	—, —	—, —

Reproductive toxicity			
̄ litters/pair	—	—	↓
# live pups/litter; pup wt./litter	—, —	—, —	↓, —
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight ^a	•	•	—, —
Sex accessory gland weight ^a (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	↑, —, —
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	not clear, 120 mg/kg	—

F ₁ generation	Dose concentration →	30 mg/kg	60 mg/kg	120 mg/kg
General toxicity	Male, female	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	—, —	↑, ↑	↑, ↑
Mortality	—, —	—, —	—, —	—, —
Adult body weight	—, —	↑, ↑	↑, ↑	↑, ↑
Kidney weight ^a	—, —	—, —	↑, ↑	↑, ↑
Liver weight ^a	—, —	↑, ↑	↑, ↑	↑, ↑
Feed consumption	•	•	•	•
Water consumption	—, —	—, —	↑, ↑	↑, ↑
Clinical signs	—, —	—, —	—, —	—, —

Reproductive toxicity			
Fertility index	—	—	↓
# live pups/litter; pup wt./litter	—, —	—, —	—, —
Absolute testis, epididymis weight ^a	—, —	—, —	—, —
Sex accessory gland weight ^a (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, —	—, —, —
Estrous cycle length	↑	↑	↑

Summary information	
Affected sex?	Not clear, perhaps female
Study confounders:	None
NOAEL reproductive toxicity:	<30 mg/kg
NOAEL general toxicity:	30 mg/kg
F ₁ more sensitive than F ₀ ?	Yes
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. ^aAdjusted for body weight.